Molecular dynamics simulation of the spontaneous formation of a small DPPC vesicle in water in atomistic detail

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SUPPORTING INFORMATION

Molecular dynamics simulation of the spontaneous formation of a small DPPC vesicle in water in atomistic detail

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0.1 Pictures of the Vesicular Aggregate and Graphs showing Properties of Lipids in the Vesicle

The supporting material includes four figures showing the structure of the vesicle and five figures showing properties of the lipids in the vesicle near the end of the simulation and of lipids in an equilibrated bilayer.

Figure 1: Transverse slices through the vesicle near the end of the simulation. Only lipids are shown. The color scheme the same as in Figure 1 of the manuscript, with the addition that terminal methyl groups of the phospholipid tails are colored blue. The seven water pores present in the vesicular wall are numbered and indicated by blue arrows.

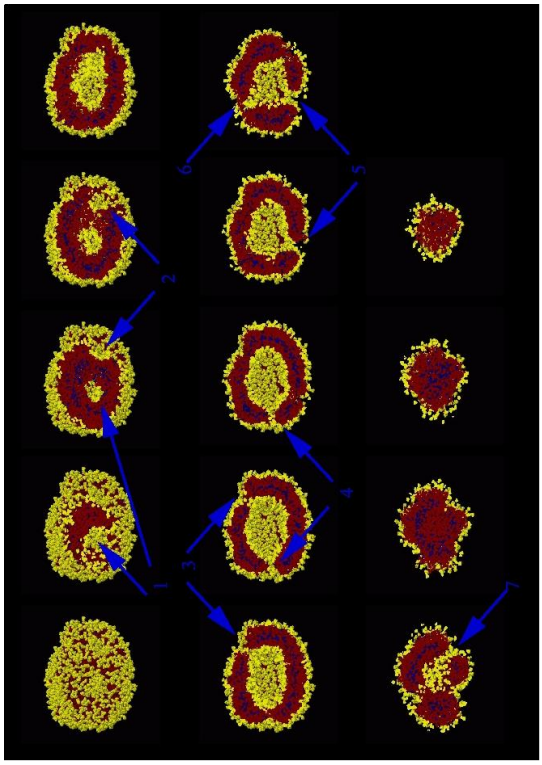


Figure 2: A thin slice through the vesicle parallel to the long axis, taken from a snapshot near the end of the simulation. Only lipids are shown; water is not shown. Furthermore, the micelle is not shown. Lipids are colored according to the leaflet they are in as follows. Outer leaflet: head groups green, tails orange, terminal methyl group brown; inner leaflet: head groups yellow, tails dark red, terminal methyl groups maroon.

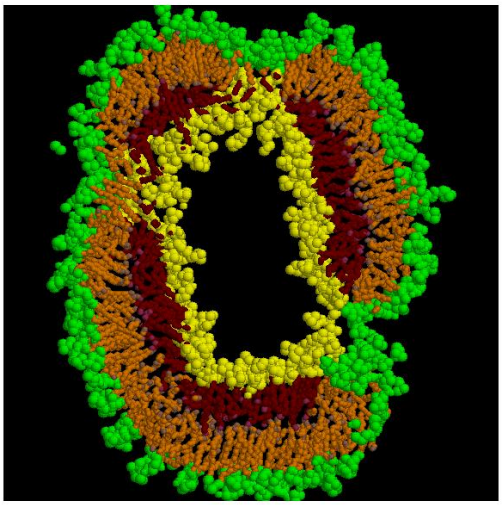


Figure 3: Transverse slice through the vesicle perpendicular to the long axis, taken from a snapshot near the end of the simulation. Only lipids are shown. The micelle is not shown. The color scheme is the same as in Figure 2. The difference in thickness between the inner and outer leaflets due to the curvature is visible.

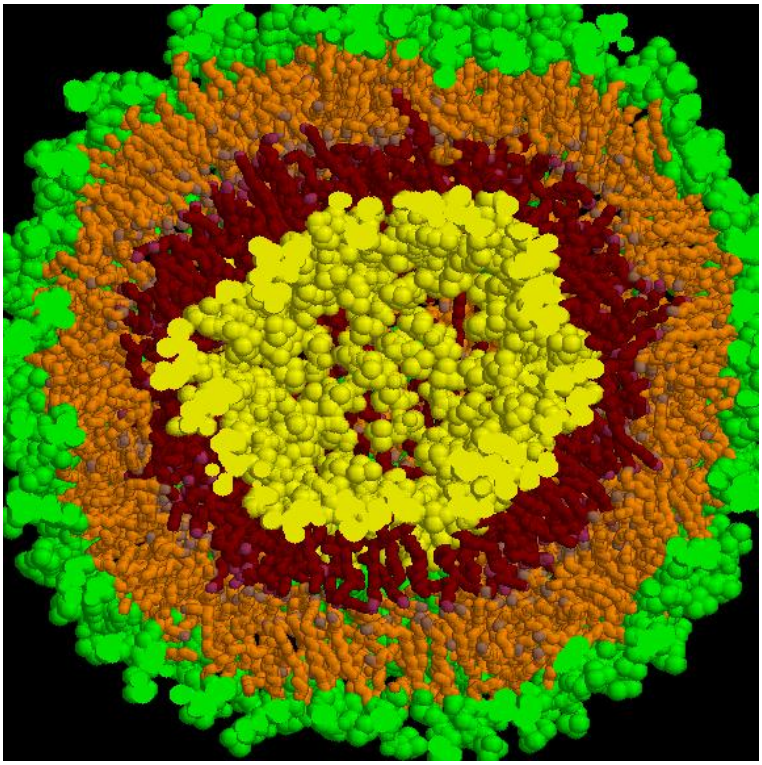


Figure 4: Close-up of the vesicular bilayer wall near the end of the simulation. The color scheme is the same as in Figure 2. The difference in the ordering of the lipid tails of the lipids in the inner and outer leaflets due to the curvature is visible. Compare to Figure 3B of the manuscript.

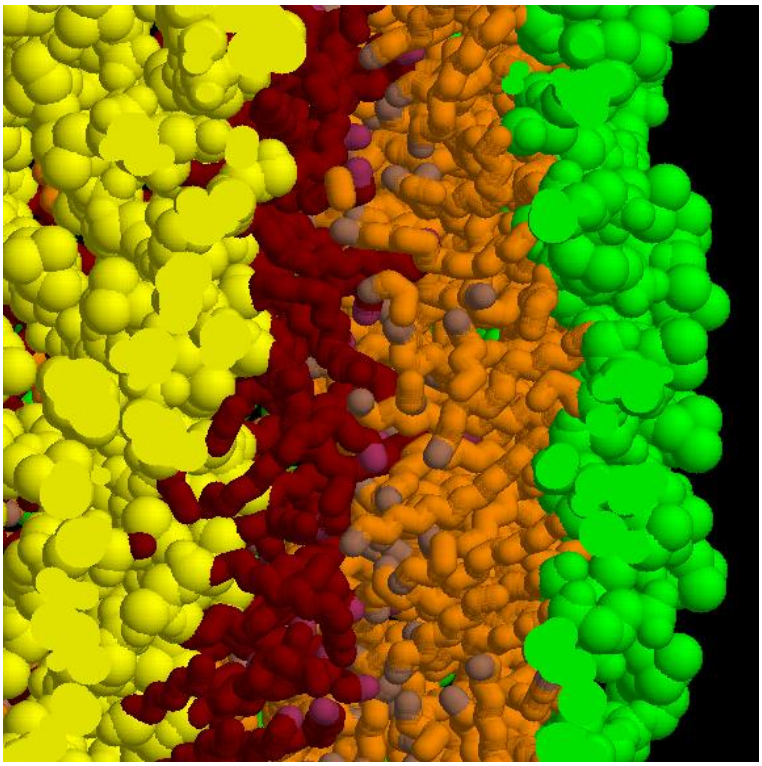


Figure 5: Order parameter profiles for the DPPC tail segments of molecules in an equilibrium bilayer (drawn line), and in the inner (dashed line) and outer (dot-dashed line) leaflets of the vesicular aggregate, with respect to the local bilayer normal. The local bilayer normal was calculated from the molecular directors of the lipid under study and its six nearest neighbor lipids. The nearest neighbor lipids were determined on the basis of the distance between the N-atoms in the head groups. The local director of a lipid was defined as the vector between the center of mass of C-atoms 6-12 of both tails and the center of mass of the atoms forming the phosphocholine moiety of the lipid head group. The order parameter profiles shown are averaged over the sn-1 and sn-2 chains. Averages were taken over 200 lipids in the inner leaflet and 600 lipids in the outer leaflet. The lines are meant to guide the eye.

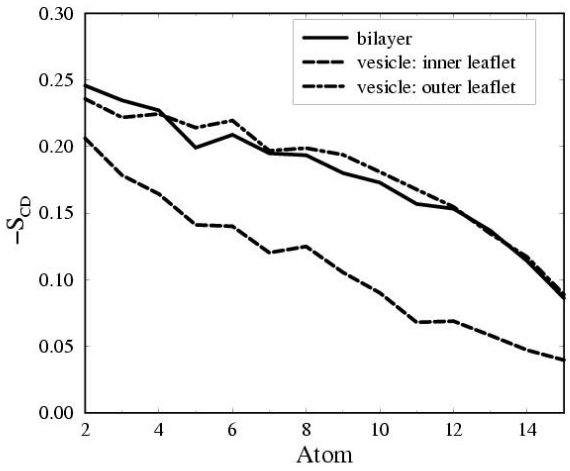


Figure 6: Head group orientation correlation as a function of distance for lipids in an equilibrated bilayer (drawn line), and in the inner (dashed line) and outer (dot-dashed line) leaflets of the vesicular aggregate. The average cosine of the angle between two vectors connecting the P- and N-atoms of two DPPC molecules, respectively, is plotted as a function of the distance between the midpoints of the two vectors. Averages were taken over 200 lipids in the inner leaflet and 600 lipids in the outer leaflet.

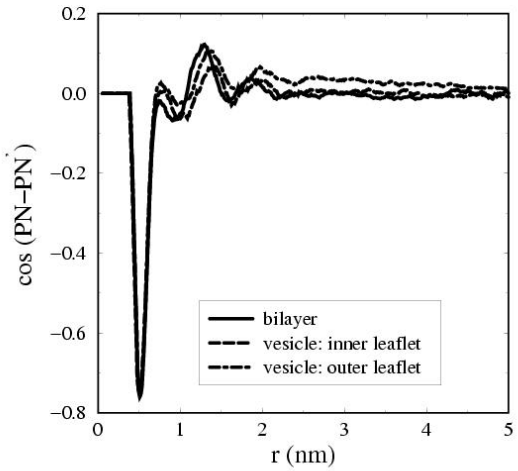


Figure 7: Radial distribution function as a function of distance, $g(r)$, for lipid N-atoms with respect to each other for lipids in an equilibrated DPPC bilayer (blue), in the inner leaflet of the vesicle near the end of the simulation (black), and in the outer leaflet of the vesicle near the end of the simulation (red), respectively. The number of N-atoms within a radial shell of radius r is also shown (dashed lines) for these three cases. The curves show the average taken over 200 lipids in the inner leaflet and 600 lipids in the outer leaflet. From the latter curves it can be seen that the density of head groups is larger in the inner leaflet of the vesicle than in the outer leaflet of the vesicle.

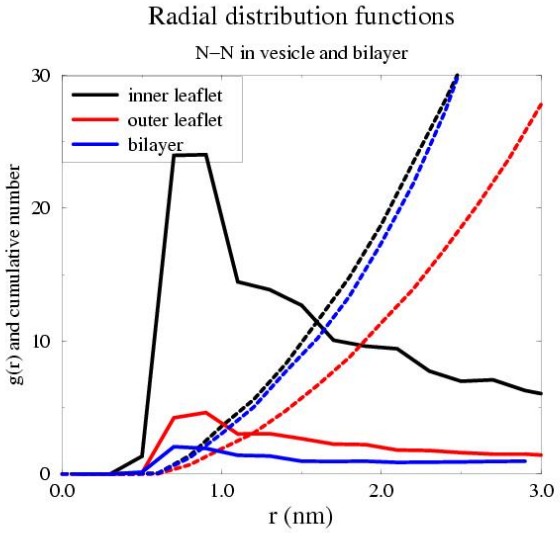


Figure 8: Radial distribution function as a function of distance, $g(r) * 10$, for water O-atoms with respect to lipid N-atoms for lipids in an equilibrated DPPC bilayer (blue), in the inner leaflet of the vesicle near the end of the simulation (black), and in the outer leaflet of the vesicle near the end of the simulation (red), respectively. The number of O-atoms within a radial shell of radius r is also shown (dashed lines) for these three cases. From the latter curves it can be seen that the hydration of the choline group is lower in the inner leaflet of the vesicle than in the outer leaflet of the vesicle.

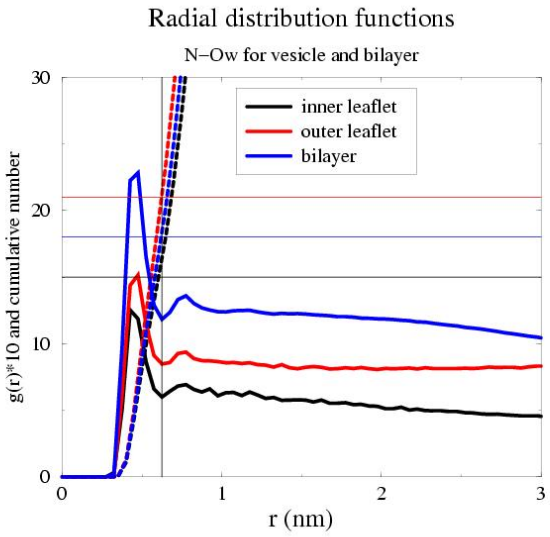
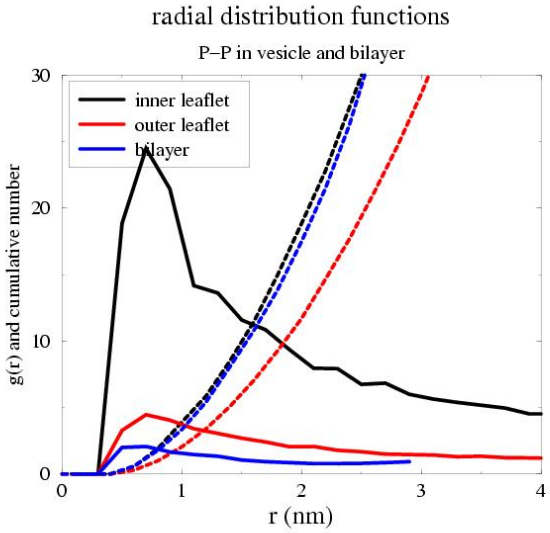


Figure 9: Radial distribution function as a function of distance, $g(r)$, for lipid P-atoms with respect to each other for lipids in an equilibrated DPPC bilayer (blue), in the inner leaflet of the vesicle near the end of the simulation (black), and in the outer leaflet of the vesicle near the end of the simulation (red), respectively. The number of P-atoms within a radial shell of radius r is also shown (dashed lines) for these three cases. From the latter curves it can be seen that the density of head groups is larger in the inner leaflet of the vesicle than in the outer leaflet of the vesicle. The curves show the average taken over 200 lipids in the inner leaflet and 600 lipids in the outer leaflet.



0.2 Simulation Set-up and Conditions Details

All simulations were performed using the GROMACS suite of code, version 3.0.5. (Lindahl, E.; Hess, B.; van der Spoel, D. *J. Mol. Mod.* **2001**, *7*, 306-317.)

force field

The force field parameters used to describe dipalmitoylphosphatidylcholine (DPPC) were taken from Berger *et al.* (Berger, O.; Edholm, O.; Jähnig, F. *Biophys. J.* **1997**, *72*, 2002.) The simple point charge (SPC) model of Berendsen *et al.* was used to model water (Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; Hermans, J. in: *Intermolecular Forces*, Pullman, B. ed., D. Reidel Publishing Company: Dordrecht, 1981.). The molecular building block definitions used in the simulations are given in the attached files with the extension .itp, and can be used with GROMACS.

simulation conditions

A Berendsen thermostat, with a coupling constant of 0.1 ps was applied in all simulations (Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F.; DiNola, A.; Haak, J. R. *J. Chem. Phys.* **1984**, *81*, 3684.). The reference temperature was set to 323 K. Pressure coupling was applied isotropically, also using the Berendsen scheme (see reference above) with a coupling constant of 1.0 ps. The reference pressure was 1 bar in all directions, and the compressibility was $5 * 10^{-5}\ bar^{-1}$. Bond lengths were constrained with the LINCS algorithm (Hess, B.; Bekker, H.; Berendsen, H. J. C.; Fraaije, J. G. E. M. *J. Comput. Chem.* **1997**, *18*, 1463.). The water geometry was constrained using the SETTLE algorithm (Miyamoto, S.; Kollman, P. A. *J. Comput. Chem.* **1992**, *13*, 952.). A time-step of 5 fs was used.

Non-bonded interactions were calculated using a twin range cut-off scheme. All Lennard-Jones and electrostatic interactions within the short-range cut-off of 1.0 nm were evaluated every time-step. Electrostatic interactions within the long-range cut-off of 1.5 nm were updated every 10 steps, together with the neighbor list. No long-range corrections were applied to the Van der Waals energy and force. Long-range electrostatic interactions were taken into account using the approximation of the moving boundary reaction field method due to Tironi *et al.* (Tironi, I. G.; Sperb, R.; Smith, P. E.; van Gunsteren, W. F. *J. Chem. Phys.* **1995**, *102*, 5451.). The relative dielectric constant used was 78.5.

The simulation conditions as used are given in the attached file vesicle.mdp, which can be used with GROMACS.

The projected area per head group of an equilibrated DPPC bilayer simulated under these conditions was 0.66 nm^2. Properties of DPPC bilayers using this force field under various other conditions, including treatment of the electrostatic interactions using Particle Mesh Ewald was described by Anézo *et al.* (Anézo, C.; de Vries, A. H.; Höltje, H.-D.; Tieleman, D. P.; Marrink, S. J. *J. Phys. Chem. B* **2003**, *107*, 9424.).

starting structure

The starting structure was generated using the GROMACS tools genbox which attempts to insert a molecule into a simulation box using randomly chosen translation and rotation of a given configuration. Eight different configurations of a single DPPC molecule were used, and the attempts were repeated as many times as deemed necessary, using different seeds for the random generator in each attempt. The initial box had an edge length of 16 nm, and was filled with 1,017 lipids. The density of the lipids was increased by a short MD run on this system without water under constant pressure conditions, shrinking the box to an edge length of 14.7 nm. The box edge length was next set to 16 nm again, and 106,563 water molecules were added to the system. After brief energy minimization, the system was left to evolve freely. The GROMACS topology file is given in vesicle.top.

```
-----------------
# this file is called ffDPPC.itp
# and contains combination rules
# and includes definition files for lipid type interactions
#
[ defaults ]
#define _FF_DPPC
#define _FF_GROMACS
#define _FF_GROMACS1
; nbfunc     comb-rule     gen-pairs     fudgeLJ     fudgeQQ
    1            2            yes          0.125       0.5
#include "ffDPPCnb.itp"
#include "ffDPPCbon.itp"
-----------------


-----------------
# this file is called ffDPPCnb.itp
# and contains lipid atom type definitions and LJ parameters
[ atomtypes ]
;name        mass      charge   ptype     sigma           epsilon
   NL  14.00670    0.000       A         0.325            0.711
   O2  15.99940    0.000       A         0.296            0.878
   OS  15.99940    0.000       A         0.300            0.711
    P  30.97380    0.000       A         0.374            0.836
    C  12.01100    0.000       A         0.375            0.438
  CH1  13.01900    0.000       A         0.380            0.334
  CH2  14.02700    0.000       A         0.396            0.380
  CH3  15.03500    0.000       A         0.396            0.570
  C3N  15.03500    0.000       A         0.396            0.606
   C2  14.02700    0.000       A         0.3905           0.494
  C2O  14.02700    0.000       A         0.380            0.494
   OW  15.99940    0.000       A         0.317            0.650
   HW   1.00800    0.000       A         0.000            0.000

[ nonbond_params ]
  ; i    j func          c6           c12
-----------------
```

```
-----------------
# this file is called ffDPPCbon.itp
# and contains lipid type bond, angle, and dihedral definitions
#
[ bondtypes ]
  ; i    j  func       b0          kb
   NL  C3N    1    0.147      376560.
   NL   C2    1    0.147      376560.
   NL    C    1    0.133      376560.
   HW    C    1    0.133      0.0
   C2  C2O    1    0.153      334720.
   C   C2O    1    0.153      334720.
   OS  C2O    1    0.143      251040.
   OS    P    1    0.161      251040.
   O2    P    1    0.148      376560.
   O2    C    1    0.123      502080.
  CH1  C2O    1    0.153      334720.
   OS  CH1    1    0.143      251040.
   OS    C    1    0.136      251040.
   OS   HW    1    0.136      0.0
   HW    C    1    0.136      0.0
    C  CH2    1    0.153      334720.
    C  CH3    1    0.153      334720.
  CH2  CH3    1    0.153      334720.
  CH2  CH2    1    0.153      334720.
   NL   O2    1    0.153      334720.
   NL   HW    1    0.153      0.0
   HW   HW    1    0.153      0.0

[ angletypes ]
  ; i    j    k func       th0         cth
  C3N   NL  C3N    1   109.5       460.24
  C3N   NL   C2    1   109.5       460.24
   NL   C2  C2O    1   109.5       460.24
   C2  C2O   OS    1   109.5       460.24
  C2O   OS    P    1   120.0       397.48
   OS    P   O2    1   109.6       397.48
   OS    P   OS    1   103.0       397.48
   O2    P   O2    1   120.0       585.76
   OS  C2O  CH1    1   111.0       460.24
  C2O  CH1   OS    1   109.5       460.24
  C2O  CH1  C2O    1   109.5       460.24
```

```
# ffDPPCbon.itp (continued)
  CH1   OS    C    1   120.0       418.40
  C2O   OS    C    1   120.0       418.40
   OS    C   O2    1   124.0       502.08
   OS    C  CH2    1   115.0       502.08
   O2    C  CH2    1   121.0       502.08
    C  CH2  CH2    1   111.0       460.24
  CH2  CH2  CH2    1   111.0       460.24
  CH2  CH2  CH3    1   111.0       460.24
  CH3    C   NL    1   111.0       460.24
; extra for tempo-attachment
  CH2    C  CH2    1   111.0       460.24
    C   NL    C    1   109.5       460.24
    C   NL   O2    1   109.5       460.24
   OS  C2O    C    1   109.5       460.24
   OS    C   NL    1   109.5       460.24
  C2O    C  CH3    1   111.0       460.24
  C2O    C   NL    1   109.5       460.24
   NL    C  CH2    1   109.5       460.24
    C   NL   O2    1   109.5       460.24
   HW    C   HW    1   109.5      0.0

[ dihedraltypes ]
  ; i    l func        q0          cq
   NL   C2    1     0.0        3.7656      3
   C2  C2O    1     0.0        5.8576      3
   OS  C2O    1     0.0        3.7656      3
   OS    P    1     0.0        1.046       3
  CH1  C2O    1     0.0        2.092       2
   OS  CH1    1     0.0        3.7656      3
   OS    C    1   180.0       16.736       2
    C  CH2    1     0.0        0.4184      6 ; ???
  CH2  CH2    1     0.0        5.8576      3


[ dihedraltypes ]
 CH2  CH2    3      9.2789   12.156   -13.120   -3.0597  26.240  -31.495
-----------------
```

```
-----------------
# this file is called vesicle.mdp
# and contains run-time variables, such as time-step,
# temperature, pressure coupling
title                    = dppc
cpp                      = /lib/cpp
integrator               = md
nsteps                   = 400000
nstlist                  = 10
nstxout                  = 5000
nstvout                  = 5000
nstxtcout                = 0
nstlog                   = 5000
dt                       = 0.005
nstenergy                = 1000
ns_type                  = grid
coulombtype              = reaction_field
epsilon_r                = 78.5
rlist                    = 1.0
rvdw                     = 1.0
rcoulomb                 = 1.5
tcoupl                   = berendsen
tc_grps                  = dppc  sol
tau_t                    = 0.1 0.1
ref_t                    = 323 323
Pcoupl                   = berendsen
pcoupltype               = isotropic
tau_p                    = 1.0
compressibility          = 5e-5
ref_p                    = 1.0
gen_vel                  = yes
gen_temp                 = 323
gen_seed                 = 17352
constraints              = all-bonds
-----------------
```

```
-----------------
# this file is called vesicle.top
# and contains the topology of the system,
;Topology for DPPC + water

; Include DPPC forcefield
#include "ffDPPC.itp"

; Include DPPC topology
#include "DPPC.itp"

; Include water topology
#include "spc.itp"

[ system ]
; Name
DPPC in Water

[ molecules ]
; Compound      #mols
DPPC            1017
SOL             106563
-----------------
```